Supplementary Material
Intrinsic (gas-phase) acidity and basicity of paracetamol

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Dedicated to Professor Rosa Maria Claramunt on the occasion of her 65th birthday

Table of Contents

Table S1. Gas-phase thermochemical quantities of reference used to determine the acidity and basicity of paracetamol [a]

	Reference acids, $A_{ref(i)}H$	***GA*, kJ·mol^{-1}**	**$\Delta_{acid}H^0$, kJ·mol^{-1}**	**$\Delta_{acid}S^0$, J·mol^{-1}·K^{-1}**
i=1	2,3,5,6-tetramethylbenzoic acid	1388.4 ± 8.4	1417.7 ± 8.8	98.4
i=2	2,2,2-trifluoroacetamide	1409.8 ± 8.4	1439.1 ± 8.8	98.4
i=3	Trimethylacetic acid	1413.5 ± 8.4	1442.8 ± 8.8	98.4
i=4	Isobutyric acid	1419.4 ± 8.4	1448.7 ± 8.8	98.4
	Average	1407.8 ± 8.4 [b]	1437.1 ± 8.8 [b]	98.4 ± 8.4 [c]
	Reference bases, $B_{ref(i)}$	***GB*, kJ·mol^{-1}**	***PA*, kJ·mol^{-1}**	**Δ_pS^0, J·mol^{-1}·K^{-1}**
i=1	1,2,3-triazole	856.7	886.8	101.2
i=2	Pyrazole	861.3	894.8	112.4
i=3	3-methylpyrazole	874.7	906.5	106.8
i=4	Benzylamine	880.1	914.0	113.8
	Average	868.2 ± 8.4 [b]	900.5 ± 8.4 [b]	108.5 ± 8.4[c]

[a] Taking from NIST Chemistry Webbook, NIST Standard Reference Database, http://webbook.nist.gov. [b] Since uncorrelated uncertainty with weighting factor (equals to $1/s_i^2$ where s_i = uncertainty experimental of i-datum) is almost ± 4 kJ·mol^{-1} while standard deviation is ± 13.5 kJ·mol^{-1}, we decided to considerer 8.4 (8.8) kJ·mol^{-1} [or 2 (2.1) kcal/mol] as accuracy of this average value, in accordance with the recommendations of NIST. [c] It is assumed to have ± 8.4 J·mol^{-1}·K^{-1} (or 2 cal/mol K) uncertainty.

Table S2. Experimental ESI conditions

	Nebulizing gas (Air)	**Drying gas**		**Potential, keV**
Reference acids	**Pressure, psi**	**Temperature, ºC**	**Pressure, psi**	**Needle**
1	10	200	10	-2.9
2	10	175	10	-3.7
3	15	225	10	-3.2
4	15	225	10	-3.3
	Nebulizing gas (N_2)	**Drying gas**		**Potential, keV**
Reference basics	**Pressure, psi**	**Temperature, ºC**	**Pressure, psi**	**Needle**
1	15	225	10	3.5
2	15	150	10	3.8
3	15	175	15	3.5
4	15	200	10	3.3

1. Determination of Gas-Phase acidity of paracetamol

Table S3. Values of ln([A⁻]/[$A_{ref(i)}^-$]) of CID products of heterodimer [A-H-$A_{ref(i)}$]⁻ of paracetamol and four reference acids, obtained at different collision center of mass - energies E_{cm}

	ln([A⁻]/[$A_{ref(i)}^-$])							
E_{cm} /eV / $A_{ref(i)}$H	**1.75**	**2.00**	**2.25**	**2.50**	**3.00**	**3.25**	**3.50**	**3.75**
1	-3.629	-3.607	-3.445	-3.415	-3.172	-3.136	-2.993	-2.855
2	-0.650	-0.642	-0.655	-0.701	-0.766	-0.691	-0.762	-0.853
3	1.248	1.111	0.951	0.855	0.569	0.495	0.351	0.212
4	2.307	2.152	1.931	1.746	1.383	1.159	1.077	0.815

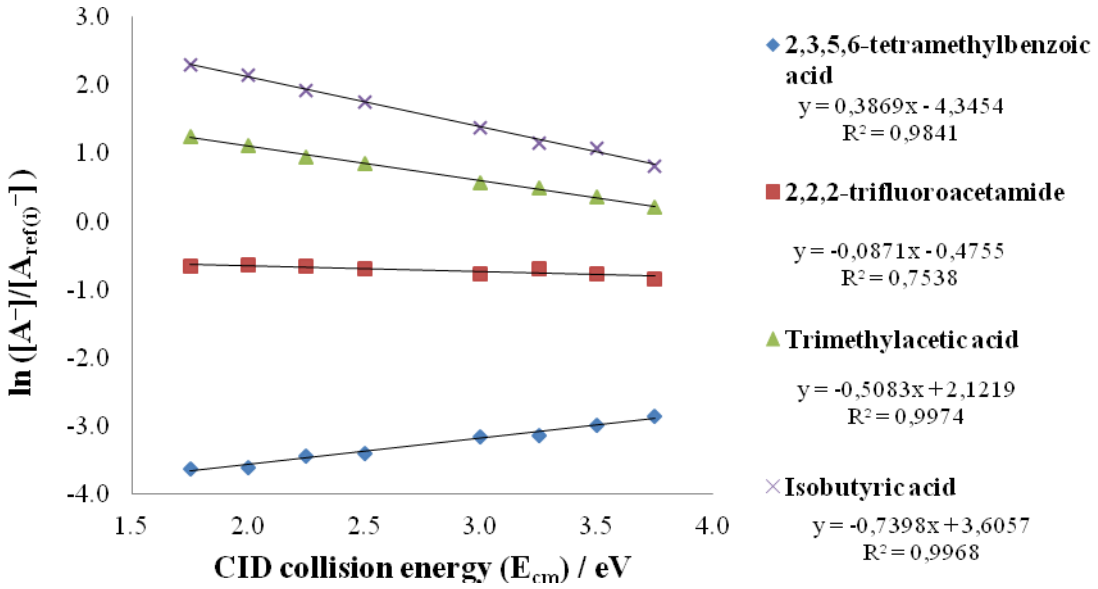

Figure S1. Plots of ln([A⁻]/[$A_{ref(i)}^-$]) of CID products of heterodimer [A·H·$A_{ref(i)}$]⁻ vs collision center of mass energies, E_{cm}

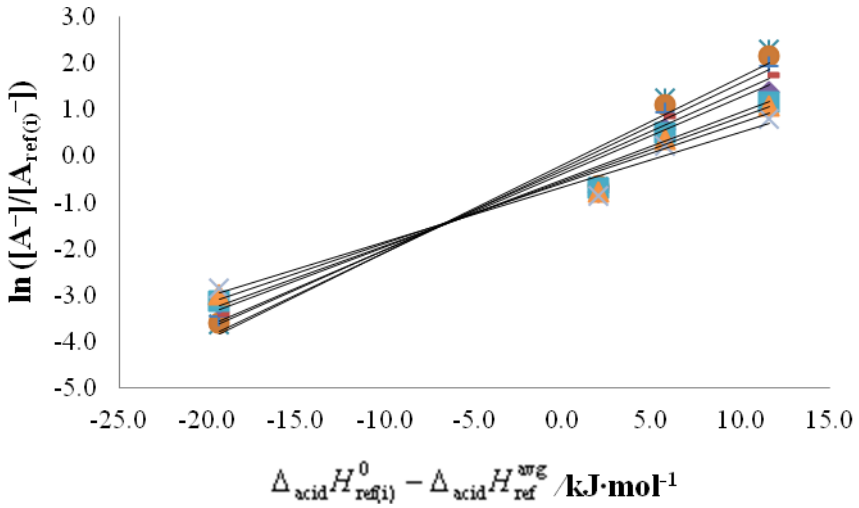

Figure S2. (a) Plots of ln([A$^-$]/[A$_{ref(i)}^-$]) vs ($\Delta_{acid}H^0_{ref(i)} - \Delta_{acid}H^{avg}_{ref}$) from dissociation of [A·H·A$_{ref(i)}$]$^-$ at eight E_{cm} collision energies.

Table S4. Values of the linear-fits obtained from data depicted in Figure S2

E_{cm} /eV	1.75	2.00	2.25	2.50	3.00	3.25	3.50	3.75
Slope	0.188	0.183	0.171	0.164	0.145	0.138	0.130	0.117
Y-intercept	-0.181	-0.246	-0.305	-0.379	-0.496	-0.543	-0.582	-0.670
R^2	0.953	0.959	0.961	0.963	0.965	0.976	0.973	0.969
T_{eff} /K	639.0	658.3	705.1	731.5	830.5	869.6	927.3	1023.7

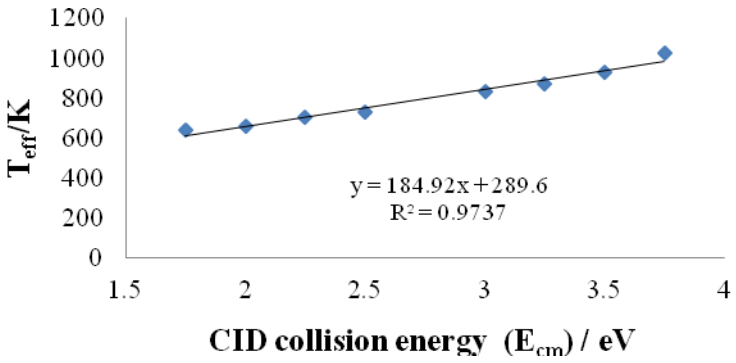

Figure S3. Plots of "effective temperature" T_{eff} against CID energies, E_{cm}.

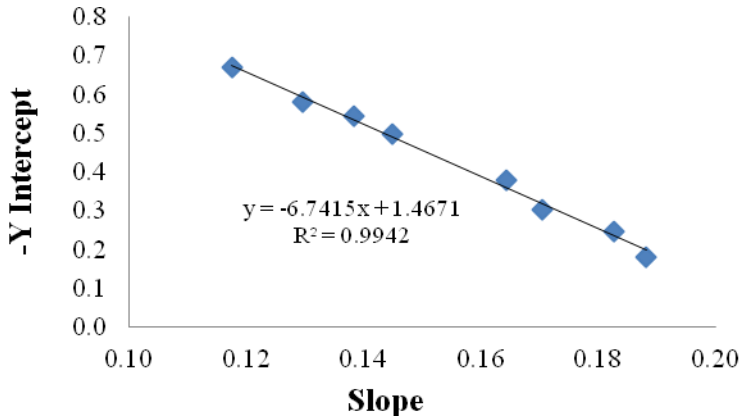

Figure S4. Plot of "–Y intercept" against "slope" values consigned in Table S4.

Table S5. Experimental deprotonation enthalpy $\Delta_{acid}H^0$, deprotonation entropy $\Delta_{acid}S^0$ and acidity GA of paracetamol

$\Delta_{acid}H^0$, kJ·mol^{-1}	$\Delta_{acid}S^0$, J·mol^{-1}·K^{-1}	$\Delta_{acid}G^0 = GA$, kJ·mol^{-1}
1430.3 ± 8.8	86.2 ± 8.4	1404.7 ± 8.8

2. Determination of Gas-Phase basicity of paracetamol

Table S6. Values of ln([BH^+]/[$B_{ref(i)}H^+$]) of CID products of heterodimer [B-H-$B_{ref(i)}$]$^+$ of paracetamol and four reference bases, obtained at different collision center of mass - energies E_{cm}

	ln([BH^+]/[$B_{ref(i)}H^+$])									
E_{cm} /eV / $B_{ref(i)}$	**0.75**	**1.00**	**1.25**	**1.50**	**1.75**	**2.00**	**2.25**	**2.50**	**2.75**	**3.00**
i = 1	4.071	3.811	2.994	2.612	2.238	1.856	1.525	1.350	0.938	0.849
2	3.231	2.973	2.238	2.113	1.602	1.356	1.297	1.094	1.050	0.646
3	-2.446	-2.592	-2.743	-2.659	-2.812	-2.702	-2.910	-2.769	-2.820	-2.789
4	-4.319	-4.254	-4.167	-4.014	-3.979	-3.957	-3.858	-3.816	-4.025	-3.778

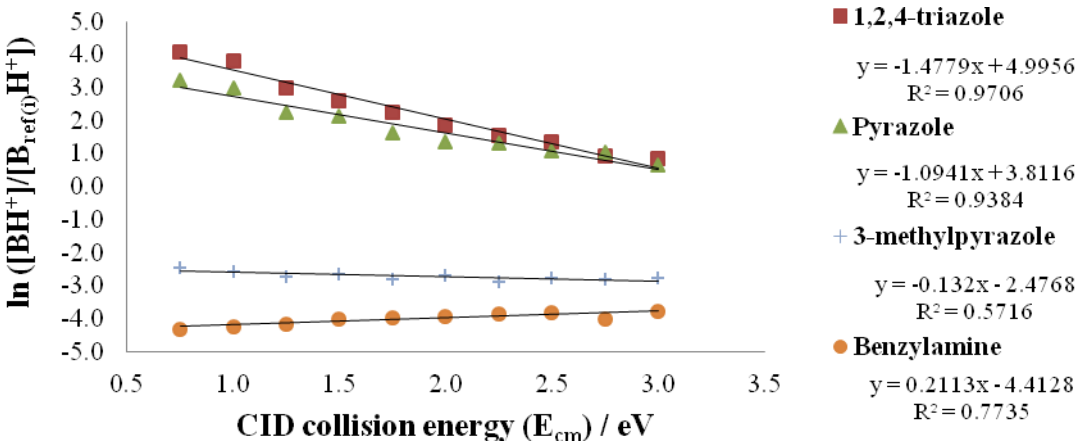

Figure S5. Plots of ln([BH^+]/[$B_{ref(i)}H^+$]) of CID products of heterodimer [$B{\cdot}H{\cdot}B_{ref(i)}$]$^+$ vs collision center of mass energies E_{cm}.

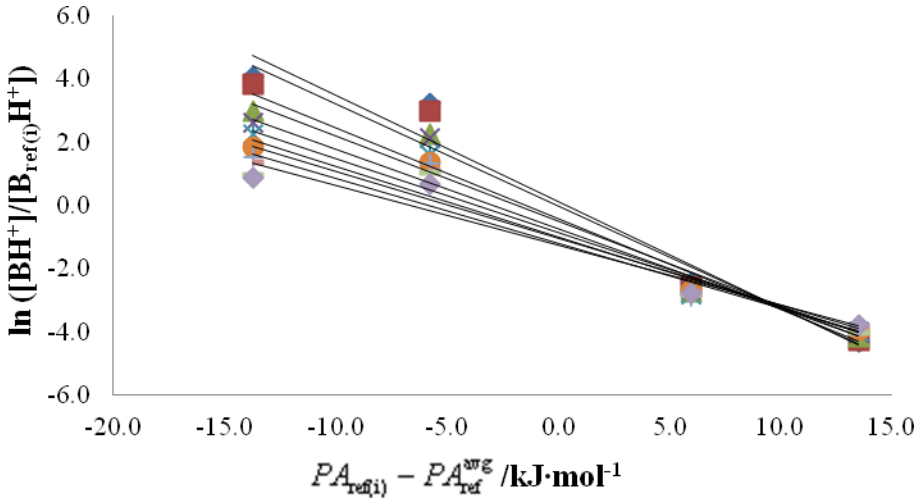

Figure S6: (a) Plots of ln([BH^+]/[$B_{ref(i)}H^+$]) vs ($PA_{ref(i)} - PA_{ref}^{avg}$) from dissociation of [$B{\cdot}H{\cdot}B_{ref(i)}$]$^+$ at ten E_{cm} collision energies.

Table S7. Values of the linear-fits obtained from data depicted in Figure S6

E_{cm}/eV	0.75	1.00	1.25	1.50	1.75	2.00	2.25	2.50	2.75	3.00
Slope	-0.336	-0.324	-0.288	-0.269	-0.251	-0.234	-0.223	-0.211	-0.205	-0.189
Y-intercept	0.134	-0.016	-0.419	-0.487	-0.738	-0.862	-0.987	-1.035	-1.214	-1.268
R^2	0.959	0.957	0.956	0.947	0.953	0.953	0.929	0.937	0.913	0.937
T_{eff}/K [(a)]	358.4	371.2	417.3	447.4	478.3	513.7	539.8	568.7	586.3	636.1

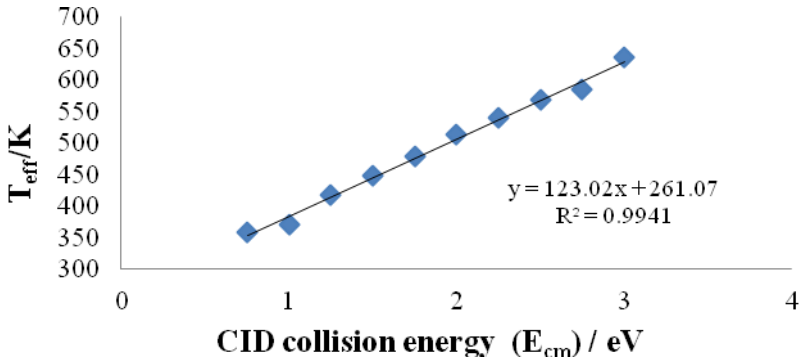

Figure S7. Plots of "effective temperature" T_{eff} against CID energies. $E_{cm.}$

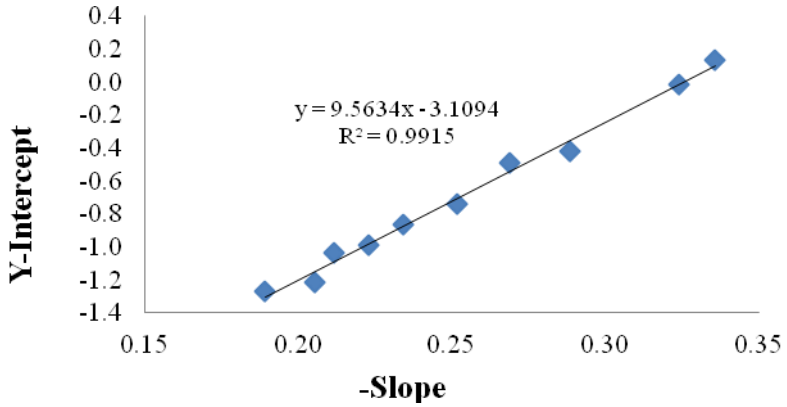

Figure S8. Plot of "Y-intercept" against "-Slope" values consigned in Table S7.

Table S8. Experimental proton affinity PA, protonation entropy Δ_pS^0 and basicity GB of paracetamol

PA. kJ·mol^{-1}	Δ_pS^0. J·mol^{-1}·K^{-1}	*GB*. kJ·mol^{-1}
909.4 ± 8.4	132.8 ± 8.4	869.9 ± 8.4